REMARKS

The Examiner is thanked for the due consideration given the application. This amendment is being filed concurrent with a Request for Continued Examination.

Claims 19-25, 27-34 and 36-47 are pending in the application. The independent claims have been amended to recite "the labeled derivative of the at least one nucleotide is within the range of 1-50 mole-% to reduce quenching and intra-molecular thiol group formation," which finds support in paragraph 0069 of the published application. The specification and claims have also been amended to recite the trade names NP-40, TWEEN 20 and TRITON X-100 as "nonionic surfactant", which is well known to persons of skill in the art. Claim 43 is new and generally corresponds to claim 19 but uses "consisting essentially of" transition language. Claims 44-47 are new and find support in the specification in, e.g., Example 1.

No new matter is believed to be added to the application by this amendment.

The Objections and Rejections have been fully addressed in the previous responses. The remarks below are provided only for points of further clarification.

Claim Objections

It is believed that the instant claims are free from informalities.

The Specification/Rejection Under 35 USC §112, First Paragraph

The specification has been objected to as containing new matter. In a linked issue, claims 32 and 41 have been rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. This rejection is respectfully traversed.

In the instant paper, the specification and claims were amended to set forth the most generic terminology for such materials as NP-40, TWEEN 20 and TRITON X-100 as "nonionic surfactant".

These materials are notoriously well known as nonionic surfactants, and the introduction of this generic terminology does not equate to new matter. Indeed, one of skill would turn to these materials only out of desire or necessity to use a nonionic surfactant.

As is noted in MPEP 608-01(v), names used in trade are permissible in patent applications if: (A) Their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or (B) in this country, their meanings are well-known and satisfactorily defined in the literature.

Now, the materials at issue have been defined and claimed as nonionic surfactants, which is well known.

Therefore, there has been no new matter introduced to the application.

Withdrawal of the objection to the specification and the written description rejection of claims 32 and 41 is accordingly respectfully requested.

Rejection Under 35 USC §112, Second Paragraph

It is believed that the instant claims are in full compliance with 35 USC § 112, second paragraph.

Rejections Based on QUAKE et al.

Claims 19-25, 31, 33, 34, 38, 40 and 42 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. (U.S. Publication No. 2002/0025529 in view of URDEA et al. (U.S. Patent 4,910,300). Claims 27, 28, 36 and 37 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al., and further in view of WELLS et al. (*J. Biol. Chem.*, vol. 261, pages 6564-6570 (1986)). Claims 30 and 39 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al., and further in view of UEMORI et al. (WO 97/24444 - taken from U.S. Patent 6,395,526) as evidenced by ATKINS (*Physical Chemistry*, 3rd Ed., Freeman and Col., New York 1986, page 278). Claims 32 and 41 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al. and further in view of HYMAN (U.S. Patent 5,516,664). Claim 42 has been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al., and further in view of WELLS et al.

These rejections are respectfully traversed.

The present invention pertains to a method for determining the sequence of a nucleic acid molecule. After providing a single-stranded form of the nucleic acid molecule, the primer is hybridized to the single-stranded form to form a template/primer complex. Then the primer is iteratively extended by the addition of a polymerase and a mixture of at least one nucleotide and at least one labeled derivative of the at least one nucleotide.

The independent claims of the present invention set forth that the at least one nucleotide is within the range of 1-50 mole-%. The utilization of this range reduces quenching and intra-molecular thiol group formation, while still allowing for efficient detection.

The important aspects of the present invention include the labeled derivative being formed from fluorophore linked to the nucleotide via a cleavable link formed from a disulfide bond.

QUAKE et al. pertain to analyzing polynucleotide sequences. The deficiencies of QUAKE et al. have been discussed in the previous response which for brevity, are not repeated here.

In short, there is no teaching or suggestion in QUAKE et al. of a percentage range of labeled nucleotide to address the problems of quenching and intra-molecular disulfide bond formation characteristic of a fluorophore-nucleotide with a disulphide linker. Indeed, it is problematic whether the

molecules of QUAKE et al., which are immobilized on the surface of a synthesis channel, possess the steric freedom to perform this chemistry.

As has been noted, there is no recognition in URDEA et al. of the specific problems of quenching and intramolecular thiol group formation that the present invention addresses.

The other applied art references do not address these deficiencies of QUAKE et al. and URDEA et al.

The Advisory Action of October 21, 2009 asserts that there is no restrictions claimed in the present invention that would define over the synthesis channels of QUAKE et al. However, it is respectfully noted that claims 22-24 of the present invention set forth a carrier that can be a gel, a solid or porous bead, a surface or a fiber.

Additionally newly added claims 44-47 of the present invention set forth that the method is performed on beads.

The Advisory Action of October 21, 2009 also asserts that the open "comprising" transitional language of the claims do not define the present invention as not utilizing a synthesis channel. However, this is only one distinction of the present invention over the prior art. But newly presented claim 43 nonetheless sets forth the present invention in more restrictive "consisting essentially of" transitional language.

Also, the present invention sets forth that the at least one nucleotide is within the range of 1-50 mole-%. The utilization of this range reduces quenching and intra-molecular thiol group formation, while still allowing for efficient detection. The Advisory Action of October 21, 2009 asserts that "Applicant has recognized another advantage which would flow naturally from following the suggestion of prior art cannot be the basis for patentability when the differences would otherwise be obvious," citing *In re Obiaya*, 227, USPQ 58, 60 BPAI 1985).

However, this is not an advantage that flows from the prior art, which does not when the differences in the prior art is considered, but rather a result that is at least unrecognized in the prior art.

That is, accidental results not intended and not appreciated do not constitute anticipation. *Eibel Processing Co. v. Minnesota and Ontario Paper Co.*, 261 US 45 (1923); *Mycogen Plant Science, Inc. v. Monsanto Co.*, 243 F.3d 1316, 1336, 5 USPQ2d 1030, 1053 (2001). Further, the Federal Circuit stated in *In re Robertson*, that "The mere fact that a certain thing may result from a set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949 (Fed. Cir. 1999). Further, it has been held that the mere fact that a certain thing may result from a given set of circumstances is not sufficient, and occasional results are not inherent. *MEHL/Biophile*

International v. Milgraum, 192 F.3d 1362, 1365, 52 USPQ2d 1303 (Fed. Cir. 1999).

The Advisory Action of October 21, 2009 further asserts that the unexpected results set forth in the specification are not commensurate in scope with the claims. Even if one assumes *arguendo* to be so, these unexpected results still have probative weight.

Both the inability to establish *prima facie* obviousness and the unexpected results should be viewed synergistically as establishing patentability of the claimed invention. "The determination of obviousness, *vel non*, requires that all the evidence be considered together . . . if rebuttal evidence of adequate weight is produced, a holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated. The objective evidence of unobviousness is not evaluated for its 'separate knockdown ability' against the 'stonewall' of the *prima facie* case . . . but is considered together with all other evidence, in determining whether the invention is as a whole would have been obvious to a person of ordinary skill in the field of the invention." (citations omitted). *Applied Materials Inc. v. Advanced Semiconductor Materials*, 98 F.3d 1563, 1574, 40 USPQ2d 1481, 1486 (Fed. Cir. 1996).

One of ordinary skill and creativity would fail to produce a claimed embodiment of the present invention from a

knowledge of QUAKE et al. and URDEA et al., and a *prima facie* case of unpatentability has thus not been made.

Further (and as has been discussed in the previous response), the present invention displays unexpected results that would rebut any unpatentability that could be alleged.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

It is believed that the rejections have been overcome, obviated or rendered moot, and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

/Robert E. Goozner/

Robert E. Goozner, Reg. No. 42,593
209 Madison Street, Suite 500
Alexandria, VA 22314
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

REG/jr